c) Remarks

The following rejections are pending as of this office action. The rejections are addressed in turn, with the rejections under § 103(a) addressed simultaneously.

1. Claims 1-3, 5, and 22-24 are rejected under 35 USC § 112, first paragraph. In addition to the claim amendments made herein, applicants respond below.

2. Claims 1-3, 5, and 22-24 are rejected under 35 USC § 103(a) as being unpatentable over U.K. Patent GB 2 294 692 A, U.K. Patent Application GB 2 306 485 A or U.S. Patent 6,117,661 to Wong et al. (hereinafter "Wong").

3. Claims 1-3, 5, and 22-24 are rejected under 35 USC § 103(a) as being unpatentable over U.S. Patent 6,100,074 to Flitsch et al. (hereinafter "Flitsch").

Claim 1 has been cancelled and replaced with new claim 25. Claim 25 is a modification of canceled Claim 1 as follows:

- to limit the sesquiterpene which is oxidized to a cyclic sesquiterpene;

- to limit the homologous enzymes to those with at least 95% sequence homology with SEQ ID NO: 1 or 24

- to limit the possible mutations which the enzymes have, and in the case of $P450_{cam}$ enzyme, this has been limited to enzymes having at least two or more particular mutations. This is based on page 6, lines 9 and 10 of the application (which state that the enzyme hay have two or more substitutions) and pages 44-46 of the application which describe enzymes with such mutations. These pages also provide basis for the reference to a mutation at position 87 of $P450_{BM-3}$ which has now been introduced into the claims.

1. Rejection of claims 1, 3-5, and 22-24 under 35 USC § 112, first paragraph

The examiner has rejected claims 1-3, 5, and 22-24 under 35 USC § 112, first paragraph,

because the examiner asserts that specification, while being enabling for a P450 enzyme of SEQ ID NOs: 1 and 24, does not reasonably provide enablement for any P450 enzyme having 90% identity to an enzyme of SEQ ID NO: 1 or 24. The examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most closely connected, to make the invention commensurate with the scope of the claims.

In light of the claim amendments made herein, applicants assert that the instant rejection has been overcome. As previously noted, claim 1 has been canceled and replaced with new claim 25. The pending claims have been limited to homologues which have at least 95% sequence homology with SEQ ID NO: 1 or 24. Given the examiner's position with respect to this rejection, as conveyed to the applicants in the interview in this application of 15 February 2005, applicants believe that this amendment will be sufficient to overcome the rejection. Accordingly, applicants respectfully request that the examiner withdraw the rejection under §112, first paragraph.

2. and 3. Rejection of claims 1, 3-5, and 22-24 under 35 USC § 103(a)over Wong and under 35 USC § 103(a) over Flitsch

The examiner has rejected claim 1, 3-5, and 22-24 under 35 USC § 103(a) over Wong, asserting that Wong teaches a method of oxidizing various substrates, including monoterpenes. The examiner asserts that Wong also teaches that the mutant P450 enzyme can oxidize a wide range of organic substrates, including terpenes or compounds containing isoprene building blocks such as terpenes, sesquiterpenes, etc. The examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to oxidize sesquiterpenes and other substrates with the mutant P450 enzyme of Wong.

The examiner has entered a substantially similar rejection of claims 1, 3-5, and 22-24 under Flitsch, asserting that Flitsch teaches a method of oxidizing various substrates, including monoterpenes and isoprenes, with mutant P450 enzymes of $P450_{cam}$ and $P450_{BM-3}$. The examiner argues that because sesquiterpenes and monoterpenes are in the class of terpene compounds, it would have been obvious to one of ordinary skill in the art to apply the teachings of Flitsch to other terpenes, such as sesquiterpenes.

Applicants respectfully traverse the rejections under § 103(a) over Wong and Flitsch. As previously noted, claim 1 has been canceled and replaced with new claim 25.

The Examiner alleges that the claims are obvious from the disclosure of one or both of Wong and Flitsch. Applicants note that the claims, as amended, refer to fewer mutations in the case of $P450_{cam}$ enzymes to particular numbers of mutations. Further, the pending claims now only refer to the oxidation of a cyclic sesquiterpene, and the oxidation of an acyclic sesquiterpene is no longer covered. Applicants assert that the pending claims, as amended, overcome the rejections under § 103(a) over Wong and/or Flitsch.

The claims define an oxidation reaction which has surprising, unexpected results and is therefore not obvious from the cited documents. As discussed in the attached declaration, the particular mutant enzymes defined in the claims have an unexpectedly high oxidation activity towards limonene, pinene and a cyclic sesquiterpene. Such high levels of oxidation are not disclosed or suggested in the cited documents which in fact have very little actual disclosure about oxidation rates, and instead mostly disclose changes in spin states for various substrates. In support of this, applicants submit herewith a Rule 132 declaration of inventor Dr. Luet Wong. Further as discussed in paragraph 5 of the declaration, the cited documents have no appreciation of the fact that different specific combinations of mutations can be used to make different oxidation products.

The declaration also discusses the structural and physical differences between isoprene and a sesquiterpene and explains that if the skilled person knew that isoprene was oxidized by a given enzyme, they would be surprised (i.e., it would not be obvious to the skilled person) that the same enzyme was also able to oxidize a sesquiterpene.

Given that the cited documents have no disclosure or suggestion that the particular $P450_{cam}$ enzymes recited in the claims have a high oxidation activity towards limonene, pinene or a sesquiterpene, and in particular provide the skilled person with no reason to assume that they would have any oxidation activity towards a sesquiterpene, then the claims are not obvious from the cited documents.

In addition, the cited documents do not contain any disclosure concerning oxidation by mutant $P450_{BM-3}$ enzymes and in particular do not disclose the high levels of oxidation of limonene, pinene or a sesquiterpene that can be achieved by $P450_{BM-3}$ enzymes with the particular mutations defined in the present claims. Therefore, this subject matter is also not obvious from the cited documents.

Accordingly, in view of the amendments and arguments provided herein and supported by the accompanying declaration of inventor Dr. Luet Wong, applicants respectfully request that the examiner withdraw the outstanding rejections under § 103(a).

d) Conclusion

In light of the Applicants' amendments and arguments, supported by the accompanying declaration of inventor Dr. Luet Wong, applicants assert that the pending claims are in condition for allowance. Applicants respectfully request withdrawal of the outstanding rejections and allowance of the pending claims. If any issues remain outstanding, please contact the undersigned for resolution of the same.

Applicants provide a check in the amount of $620.00 for this response ($395.00 for a request for continued examination and $225.00 for a two-month extension of time). Applicants believe that no other fees are associated with the filing of this response. However, if Applicants are in error, the Commissioner is hereby authorized to charge any additional fees associated with this filing from Deposit Account No. 06-2375, under Order No. P02196US0/10104571 from which the undersigned is authorized to draw.

Date: May 16, 2005

Respectfully submitted,

By _____

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